IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF TEXAS
HOUSTON DIVISION

GAYATHRI MURTHY, Plaintiff, v. ABBOTT LABORATORIES, Defendant.	)	Case No. 4:11-cv-00105-KPE Hon. Keith P. Ellison

DEFENDANT ABBOTT LABORATORIES'
MOTION FOR SUMMARY JUDGMENT ON CAUSATION

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STATEMENT OF THE NATURE AND STAGE OF THE PROCEEDING

In this diversity-jurisdiction case, plaintiff (a Texas resident) brings failure-to-warn and breach of contract claims, alleging that Abbott Laboratories' ("Abbott") prescription drug Humira caused her lymphoma. Fact and expert discovery have been completed. This motion addresses plaintiff's failure to create material issues of fact to establish that her lymphoma was caused by Humira. It is filed as a companion to Abbott's Motion to Exclude Causation Testimony Under Federal Rule of Evidence 702.

STATEMENT OF THE ISSUES

1. A toxic tort plaintiff cannot raise a genuine issue of fact on general causation under Texas law without at least two epidemiologic studies demonstrating a statistically-significant doubling of the risk. Plaintiff's experts fail to offer even one such study, and admit that numerous epidemiologic studies consistently find no causal link between Humira and lymphoma. Does plaintiff's lack of epidemiologic evidence to support general causation require summary judgment?

2. Plaintiff must exclude other plausible causes of her disease with reasonable certainty under Texas law. Plaintiff's specific causation expert concedes that he cannot exclude multiple other causes of plaintiff's lymphoma, including plaintiff's rheumatoid arthritis, which he admits put her at eight times greater risk of developing this disease, and idiopathic causes, which he concedes are responsible for more than 80-90% of reported cases. Does plaintiff's admitted inability to exclude other plausible causes of her disease require summary judgment?

STANDARD OF REVIEW

A district court "shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). Rule 56 requires that, when a properly supported motion for

summary judgment is made, the nonmoving party must "set forth specific facts showing that there is a genuine issue for trial." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 250 (1986). The nonmovant's "burden will not be satisfied by 'some metaphysical doubt as to the material facts, by conclusory allegations, by unsubstantiated assertions, or by only a scintilla of evidence." *Boudreaux v. Swift Transp. Co.*, 402 F.3d 536, 540 (5th Cir. 2005) (citation and quotation marks omitted). Rather, there must be "evidence . . . such that a reasonable jury could return a verdict for the nonmoving party." *Seacor Holdings, Inc. v. Commonwealth Ins. Co.*, 635 F.3d 675, 680 (5th Cir. 2011).

SUMMARY OF THE ARGUMENT

Plaintiff alleges that she developed lymphoma as a result of taking Humira, a tumor necrosis factor-α ("TNF") inhibitor (or "anti-TNF") that her doctor prescribed to successfully treat her rheumatoid arthritis. Plaintiff seeks compensation for a disease that her own experts admit is associated with her underlying rheumatoid arthritis and that numerous studies have consistently found is ***not*** associated with Humira.[1] To prevail, "plaintiff must demonstrate both general causation and specific causation." *Burton v. Wyeth-Ayerst Labs. Div. of Am. Home Prods. Corp.*, 513 F. Supp. 2d 719, 729 n.13 (N.D. Tex. 2007).

Plaintiff's own experts admit that there is no scientific evidence demonstrating general causation: that anti-TNF therapies such as Humira cause lymphoma. They concede that there is not a single full-length, peer-reviewed study finding a statistically significant association between anti-TNF agents and lymphoma—much less the multiple studies required to establish causation under the Texas Supreme Court's decisions in *Merrell Dow Pharm., Inc. v. Havner*,

[1] The potential risk of lymphoma was nonetheless the subject of an express warning in the Humira labeling—a warning of which plaintiff's physician was fully aware, and which was the subject of a disclosure she signed before taking Humira. These warnings bar plaintiff's claims, as explained in Abbott's summary judgment motion based on the learned intermediary doctrine, but—irrespective of the Humira warnings—plaintiff's claims also fail for the independent reason that she cannot show that Humira *can* cause lymphoma, let alone that it *did* so in her case.

953 S.W.2d 706 (Tex. 1997) and *Merck & Co. v. Garza*, 347 S.W.3d 256 (Tex. 2011). Indeed, the more than twenty epidemiological studies that have examined this issue affirmatively ***refute*** plaintiff's allegations—consistently demonstrating that there is ***no*** association between anti-TNFs and such disease. That is also the published conclusion of plaintiff's sole general causation expert, who reviewed the available literature and concluded that there is "no causal link" between anti-TNFs and lymphoma.[2] Plaintiff cannot meet her threshold burden to show that Humira is capable of causing lymphoma.

Nor can plaintiff meet her burden to demonstrate specific causation: that Humira actually caused lymphoma in plaintiff's case. As plaintiff's experts acknowledge, rheumatoid arthritis itself can cause lymphoma independent of any treatment. And plaintiff's specific causation expert, Dr. Dean McCracken, expressly concedes that he cannot rule out plaintiff's rheumatoid arthritis—which he admits increased her risk of lymphoma more than 8-fold—as the sole cause of her disease. Dr. McCracken further acknowledges that more than 80-90% of cases of lymphoma are idiopathic—*i.e.*, due to causes that are unknown—and that it is "impossible" to rule out such causes in a case like Ms. Murthy's. Accordingly, plaintiff cannot meet the requirements for establishing specific causation under well-settled Texas and Fifth Circuit law.

Based on these admissions alone, the Court may grant summary judgment without reaching defendant's accompanying *Daubert* motion on causation. Even taking plaintiff's experts' testimony at face value, the scientific evidence affirmatively refutes plaintiff's causation claims.

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[2] App. 12, Kong et al., *Potential Adverse Events with Biologic Response Modifiers*, 5 Autoimmunity Reviews 471, 478, 482 (2006). "App. __" refers to an exhibit included in the Omnibus Appendix in Supp. of Def's Mot. for Summary Judgment on Failure-to-Warn and Breach-of-Contract Claims, Mot. for Summary Judgment on Causation, Mot. to Exclude Causation Testimony, and Mot. to Exclude the Testimony of Michael Hamrell, Ph.D.

BACKGROUND

I. Humira Is A Revolutionary Therapy That Provides Significant Benefits To Patients Suffering From Rheumatoid Arthritis And Other Autoimmune Conditions.

Humira (generic name adalimumab) is a member of the class of drugs known as "anti-TNFs" or "TNF inhibitors." Anti-TNF agents are FDA-approved prescription medicines indicated for a range of autoimmune conditions, including rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriasis, psoriatic arthritis, and ulcerative colitis.[3] All of plaintiff's experts agree that these products constitute a revolutionary therapy[4] that provides "significant benefits"[5] to patients with these debilitating conditions, and are "excellent drugs to treat rheumatoid arthritis."[6] As a result, the medical community now considers them a "cornerstone of therapy" for patients with rheumatoid arthritis and other autoimmune conditions.[7]

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[3] App. 4, American College of Rheumatology, *Anti-TNF* (2012) at 1.

[4] *See* App. 53, Gershwin *Calisi* Dep. at 101; *see also id.* at 62 (agreeing that "anti-TNF agents have revolutionized the treatment of rheumatoid arthritis and other medical conditions"); *id*. at 101 (agreeing that "the TNF inhibitors are . . . much more effective than the drugs that were in existence before TNF inhibitors").

[5] *Id.* at 61; *see also id.* at 25 (anti-TNFs are "very effective and they can produce great benefit to patients"); App. 62, McCracken Dep. at 37-39 (agreeing that "Humira and other anti-TNF agents provide patients with significant benefits" and are a "significant medical advance"); *id.* at 47 (agreeing that "[t]here's no question that Humira has positive benefits for patients"); App. 56, Gershwin *Tietz* Dep. at 13 (agreeing that "anti-TNF agents, including Humira, have led to significant therapeutic advances in our treatment of patients with autoimmune disease, including rheumatoid arthritis"); App. 55, Gershwin Dep. at 182 (biologics have "dramatically improved the care of patients with rheumatic disease").

[6] App. 53, Gershwin *Calisi* Dep. at 73 ("I would agree that Humira and the other anti-TNFs are excellent drugs to treat rheumatoid arthritis."); *see also* App. 65, Popovich Dep. at 165, 23 (Humira and other anti-TNFs have "revolutionized the field of rheumatology" and today are the "cornerstone therapy" for treating rheumatoid arthritis—"a severe and potentially crippling disease"); *id.* at 164-65 (medications available before anti-TNFs could not "control the underlying disease," and as a result, "many of [the patients] would develop erosions . . . and progress to disability over 10 years, 15 years"; anti-TNFs "arrest[] some of the joint damage and improv[e] [the patients'] functional ability," and have "made a big impact on the patient's life and [a] big impact in the rheumatology practice overall").

[7] App. 22, Solomon et al., *Observational Studies on the Risk of Cancer Associated with Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: A Review of Their Methodologies and Results,* 64 Arthritis & Rheumatism 21, 21 (2012) (TNF inhibitors "have proven to be highly effective in the treatment of various autoimmune conditions, including rheumatoid arthritis (RA). Indeed, according to several international guidelines that were based on abundant evidence from therapeutic trials and clinical experience, these agents have come to be considered a cornerstone of therapy for patients with RA that is severe or refractory to treatment.").

According to her treating physician, Humira provided Ms. Murthy in particular with significant benefits. Ms. Murthy's rheumatologist, Dr. Jovan Popovich, diagnosed her with rheumatoid arthritis in September 2004.[8] In January 2005, Dr. Popovich added Humira to her existing rheumatoid arthritis therapy.[9] Dr. Popovich reported that Humira helped alleviate Ms. Murthy's rheumatoid arthritis and she was "doing well" while on it.[10]

Ms. Murthy discontinued Humira therapy when she was diagnosed with lymphoma in February 2006.[11] After approximately three months of treatment, her lymphoma was in complete remission and it remains so, over seven years later.[12] Despite the fact that plaintiff's own experts agree that her rheumatoid arthritis or other factors alone could have caused her lymphoma, plaintiff's complaint alleges that her lymphoma was caused by Humira.[13]

II. The Scientific Community Has Thoroughly Studied Whether There Is Any Relationship Between Anti-TNFs And Lymphoma.

The scientific community has thoroughly studied whether Humira and other anti-TNFs are associated with lymphoma. Like other anti-TNFs, Humira is a "biological product," and received FDA approval pursuant to the biologics licensing application ("BLA") process outlined at 42 U.S.C. § 262(a) *et seq.*, which included extensive clinical trials.[14] The FDA approved

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[8] *See* App. 65, Popovich Dep. at 170.

[9] Dkt. 115, Second Amended Complaint ¶ 2.

[10] *See* App. 65, Popovich Dep. at 93, 95.

[11] Dkt. 115, Second Amended Complaint ¶¶ 40-41; App. 67, Samaniego Dep. at 21 (Ms. Murthy "stopped both medications [Humira and methotrexate] after [she was] diagnosed with lymphoma.").

[12] Dkt. 115, Second Amended Complaint ¶ 43; App. 67, Samaniego Dep. at 31 (agreeing that "Ms. Murthy was diagnosed on 2-27-06 but complete remission was revealed on 5-18-06").

[13] Dkt. 115, Second Amended Complaint ¶ 2.

[14] Although approved through the BLA process (as opposed to a New Drug Application or "NDA"), the relevant FDA regulations and case law relating to NDAs and FDA-approved drugs are applicable to biological products, like Humira. *See* 42 U.S.C. § 262(j) ("The Federal Food, Drug, and Cosmetic Act . . . applies to biological product subject to regulation under this section."); *see also, e.g.*, App. 112, 21 C.F.R. § 201.56(b) ("Categories of prescription drugs subject to the labeling content and format requirements in §§ 201.56(d) and 201.57" include "[p]rescription drug products for a new drug application (NDA), biologics license application (BLA), or efficacy

Humira as a safe and effective treatment for rheumatoid arthritis in December 2002.[15] Humira was the third anti-TNF drug approved for treating rheumatoid arthritis,[16] after the FDA approved Remicade and Enbrel to treat Crohn's disease and rheumatoid arthritis, respectively, in 1998,[17] and approved Remicade for rheumatoid arthritis in 1999.[18]

Before the FDA approved Humira, the issue of whether there was a relationship between anti-TNFs and lymphoma was already a matter of widespread attention, especially in rheumatoid arthritis patients like plaintiff. It was well known that patients with rheumatoid arthritis experienced an increased incidence of lymphoma as a result of their disease alone—independent of any treatment they received[19]—and that this risk increases with disease severity.[20] Even outside the context of rheumatoid arthritis, lymphomas are one of the most common cancers in the general population[21]—most resulting from causes that are unknown.[22] Accordingly, it was

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supplements . . . ."). Plaintiff's expert agrees that the "officials at FDA who reviewed" and "who approved" the Humira BLA "were qualified by training and experience to conduct those reviews and make that determination." App. 58, Hamrell *Calisi* Dep. at 69-70, 79, 99-100.

[15] App. 43, 12/31/2002 Humira label at ABT 01614265 - ABT 01614293.

[16] *Id.* at ABT 01614265; App. 53, Gershwin *Calisi* Dep. at 241-42.

[17] App. 46, 11/10/1999 Remicade label at 6; App. 42, 11/02/1998 Enbrel label at 3.

[18] App. 46, 11/10/1999 Remicade label at 6.

[19] *See, e.g.*, App. 5, Baecklund et al., *Disease Activity and Risk of Lymphoma in Patients with Rheumatoid Arthritis: Nested Case-Control Study*, 317 BMJ 180, 181 (1998); App. 8, Brown et al., *Tumor Necrosis Factor Antagonist Therapy and Lymphoma Development: Twenty-Six Cases Reported to the Food and Drug Administration*, 46 Arthritis & Rheumatism 3151, 3151 (2002); App. 6, Baecklund et al., *Association of Chronic Inflammation, Not Its Treatment, With Increased Lymphoma Risk in Rheumatoid Arthritis*, 54 Arthritis & Rheumatism 692, 692 (2006); App. 2, Askling et al., *Anti-Tumour Necrosis Factor Therapy in Rheumatoid Arthritis and Risk of Malignant Lymphomas: Relative Risks and Time Trends in the Swedish Biologics Register*, 68 Annals of the Rheumatic Disease 648, 648 (2009); App. 10, Cush et al., *Does Rheumatoid Arthritis or Biologic Therapy Increase Cancer Risk?*, 4(2) Drug Safety Quarterly 1, 1 (2012); App. 16, Mariette et al., *Malignancies Associated with Tumour Necrosis Factor Inhibitors in Registries and Prospective Observational Studies: A Systematic Review and Meta-Analysis*, 70 Annals of the Rheumatic Disease 1895, 1895 (2011).

[20] App. 10, Cush et al. (2012) at 1-3. Among other things, diseases such as rheumatoid arthritis involve "[l]ong-lasting inflammatory activity," which is a well-recognized risk factor for lymphoma. App. 15, Mariette et al., *Lymphoma in Patients with Anti-TNF: Results of the 3-Year Prospective French RATIO Registry*, 69 Annals of the Rheumatic Disease 400, 400 (2010); *see also* App. 53, Gershwin *Calisi* Dep. at 304, 49.

[21] App. 3, The American Cancer Society, *Lifetime Risk of Developing or Dying from Cancer* (2011), at 3; *see also* App. 62, McCracken Dep. at 103 (agreeing that diffuse large B cell lymphoma is "a very common type of

not surprising that, when the FDA approved anti-TNF therapies for use in moderate-to-severe rheumatoid arthritis patients, there were case reports of lymphomas appearing in such an at-risk patient population. Nonetheless, the question remained whether anti-TNFs increased the risk of lymphoma beyond the already-elevated background incidence for such patients.

The FDA took up the task of addressing this question well before it approved Humira, convening at least three public advisory committee meetings[23] between 1998 and 2001.[24] At these meetings, FDA reviewers and advisory committee members—doctors, scientists and regulators—discussed a "theoretical concern" about "the inhibition of TNF" in the "area of cancer,"[25] and emphasized that the role of TNF inhibitors in the development of lymphoma was unknown.[26] The committee participants further highlighted the difficulty of teasing out established lymphoma risks associated with the underlying disease of RA versus any additional incremental risks potentially associated with TNF inhibitors.[27] Nevertheless, because the relationship between anti-TNFs and lymphoma was difficult to assess, the FDA concluded that all such therapies should warn of the potential relationship with lymphoma. Abbott's Humira thus included FDA-approved warnings from the date it was approved for sale.[28]

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lymphoma in rheumatoid arthritis patients."); *id.* at 22 (agreeing that "there are a lot of people who develop lymphoma who are never on anti-TNFs.").

[22] App. 53, Gershwin *Calisi* Dep. at 187; App. 62, McCracken Dep. at 98.

[23] *See* App. 40, *Final Guidance, Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: The Open Public Hearing at FDA Advisory Committee Meetings*, at 1-2 (Dec. 2010).

[24] App. 30, 09/16/1998 FDA Transcript at 57; App. 29, 05/28/1998 FDA Transcript at 187, 84, 247; App. 33, 08/17/2001 FDA Transcript at 52, 89-90, 152.

[25] App. 30, 09/16/1998 FDA Transcript at 57.

[26] App. 29, 05/28/1998 FDA Transcript at 187, 84, 247.

[27] *Id.* at 247. As Barbara Frank, M.D, Acting Chair of the May 1998 meeting, observed: "The data that we have, the cases that we have, and we don't know the primary disease versus the therapy." *Id.*

[28] App. 43, 12/31/2002 Humira label at 12.

In 2002, shortly after Humira came to market, the FDA published a review of the 26 cases of lymphoma that had been reported in patients taking Enbrel or Remicade, noting that there were many potentially confounding factors and alternative causes:

> Currently available data do not permit us to draw definitive conclusions regarding whether these TNF antagonists were the proximate cause of the reported lymphomas, whether these neoplasms developed as part of the natural history of the underlying medical conditions, or whether they occurred as a complication relating to other immunosuppressive medications to which these patients were exposed.[29]

The FDA again noted that a causal relationship between anti-TNFs and lymphoma had *not* been established: "A case series such as this cannot establish a cause-and-effect relationship between drugs, such as etanercept and infliximab, and an adverse outcome, such as lymphoma."[30]

III. Scientific Evidence Confirms that Humira Does Not Cause Lymphoma.

The science has come far in the last decade. Since Humira's approval, researchers have published over twenty peer-reviewed epidemiological studies examining whether anti-TNFs can cause lymphoma. These studies have consistently found ***no*** statistically significant relationship between lymphoma and anti-TNF therapy.[31] Recent reviews of the data by leading experts have

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[29] App. 8, Brown et al. (2002) at 3155.

[30] *Id.* at 3156.

[31] These studies are discussed in greater detail in the accompanying report of defendant's expert, Dr. Howard Ory, an epidemiologist and physician with twenty-three years' experience working at the U.S. Centers for Disease Control, including as Deputy Director for Research in the Epidemiology Program Office and Chief of the Epidemiologic Studies Branch of the Family Planning Division. App. 50, Ory Expert Report.

As explained in Dr. Ory's report, epidemiologic studies often report the strength of an association between exposure and disease in terms of a "relative risk" and a "confidence interval." Relative risk "describes the increased or decreased incidence of the disease in question in the population exposed to the factor as compared to the control population not exposed to the factor." *Brock v. Merrell Dow Pharm., Inc.*, 874 F.2d 307, 312 (5th Cir. 1989). The confidence interval reports the range of possible values calculated from the results of a study or, "in simple[r] terms, the [study's] 'margin of error.'" *In re Bextra & Celebrex Mktg. Sales Practices & Prods. Liab. Litig.*, 524 F. Supp. 2d 1166, 1174 (N.D. Cal. 2007). "The generally accepted . . . confidence level in epidemiological studies is 95%, meaning that if the study were repeated numerous times, the confidence interval would indicate the range of relative risk value that would result 95% of the time." *Havner*, 953 S.W.2d at 723. "[I]f the [confidence] interval includes the number 1.0, the study is not statistically significant, or, said another way, is inconclusive." *Id.*; *Brock*, 874 F.2d at 313 ("find[ing] . . . results inconclusive due to the fact that the confidence interval include[s] 1.0[.]"). Thus, to show a statistically-significant doubling of the risk, the study must at least: (1) demonstrate a relative risk of over

thus concluded that this large body of epidemiological data demonstrates that anti-TNF therapies such as Humira do not cause lymphoma or increase lymphoma risk. For example, a 2012 review of the scientific literature by researchers at Harvard University, Brigham and Women's Hospital and the University of California, San Diego reported that the studies showed "a consistent lack of association between anti-TNFs and cancer[.]"[32] Another 2012 review by one of the members of the FDA's Advisory Committee on Arthritis Drugs in the American College of Rheumatology's *Drug Safety Quarterly* came to the same conclusion, reporting that there is no evidence that anti-TNFs "impart an added risk of lymphoma."[33] As the review noted, "[n]umerous observational studies and metanalyses have demonstrated that . . . RA patients receiving biologic therapies [such as Humira] have the same lymphoma risk as do RA patients treated with methotrexate (MTX) or other non-biologic DMARDs."[34] Moreover, "[t]he risk of developing lymphoma or other malignancies during treatment with a TNF inhibitor does not increase over time."[35]

Accordingly, in the decade since the FDA approved Humira, no regulatory agency, health care organization, or peer-reviewed study has ever concluded that Humira or other anti-TNFs cause lymphoma or increase lymphoma risk in patients with rheumatoid arthritis, like Ms. Murthy. To the contrary, as the researchers observed, "[p]atients with RA treated with TNF antagonists did not have higher lymphoma risks than other patients with RA;" and, as studies

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2.0; (2) not include a confidence interval of 1.0; and (3) have a confidence level of at least 95%. *See Havner*, 953 S.W.2d at 721 (for the result "to indicate a doubling of the risk, the relative risk must be greater than 2.0").

[32] *See* App. 22, Solomon et al. (2012) at 29 ("[W]e observed (in our review) a consistent lack of association between TNF inhibitors and cancer across the 11 reports included."); *id.* at 26 Table 2 (reporting confidence intervals with lower bounds ranging from .5 to .9 for lymphoma risk).

[33] App. 10, Cush et al. (2012) at 2. As plaintiff's expert Dr. Gershwin acknowledged, the American College of Rheumatology "is the foremost organization of rheumatologists in the country." App. 53, Gershwin *Calisi* Dep. at 299.

[34] App. 10, Cush et al. (2012) at 2.

[35] *Id.*; *see also id.* at 3 ("Biologic-treated RA patients have similar rates of lymphoma and of lung and skin cancer as do non-biologic DMARD-treated RA patients.").

accumulated, there was "strong evidence that lymphoma is not increased among RA patients treated with anti-TNF agents."[36] For example:

- **Wolfe & Michaud (2004):** "[D]ata are insufficient to establish a causal relationship between RA treatments and the development of lymphoma."[37]

- **Askling et al. (2005):** "Patients with RA treated with TNF antagonists did not have higher lymphoma risks than other patients with RA."[38]

- **Setoguchi et al. (2006):** "We found no significant increase in the risk of cancers [including lymphoproliferative disorders] in biologic DMARD users."[39]

- **Wolfe & Michaud (2007):** "The results of this study provide strong evidence that lymphoma is not increased among RA patients treated with anti-TNF agents in routine clinical practice, and is in agreement with the linked cancer registry reports from Sweden by Askling et al." "In a study of lymphoma in 19,591 RA patients over 89,710 person-years of follow-up, which included exposure to anti-TNF therapy in 10,815 patients, we did not observe evidence for an increase in the incidence of lymphoma among patients who received anti-TNF therapy."[40]

- **Askling et al. (2009):** "No increase [in lymphoma risk] was observed among RA patients first starting anti-TNF therapy in 2002 or later . . . . [W]e noted no increase in lymphoma risk shortly after the start of anti-TNF therapy, nor any increase in lymphoma risk with increasing time since treatment start, accumulated time on active anti-TNF therapy, or by any particular anti-TNF drug."[41]

- **Mariette et al. (2010):** "Three cohorts of RA patients have been used to compare treatment with anti-TNF agents and with classic disease-modifying antirheumatic drugs in terms of the risk of lymphoma; and did not find an increased risk with anti-

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[36] App. 1, Askling et al., *Haematopoietic Malignancies in Rheumatoid Arthritis: Lymphoma Risk and Characteristics After Exposure to Tumour Necrosis Factor Antagonists*, 64 Annals of the Rheumatic Disease 1414, 1414 (2005); App. 24, Wolfe & Michaud, *The Effect of Methotrexate and Anti-Tumor Necrosis Factor Therapy on the Risk of Lymphoma in Rheumatoid Arthritis in 19,562 Patients During 89,710 Person-Years of Observation*, 56 Arthritis & Rheumatism 1433, 1439 (2007).

[37] App. 23, Wolfe & Michaud, *Lymphoma in Rheumatoid Arthritis: The Effect of Methotrexate and Anti-Tumor Necrosis Factor Therapy in 18,572 Patients*, 50 Arthritis & Rheumatism 1740, 1740 (2004).

[38] App. 1, Askling et al. (2005) at 1414.

[39] App. 20, Setoguchi et al., *Tumor Necrosis Factor α Antagonist Use and Cancer in Patients with Rheumatoid Arthritis*, 54 Arthritis & Rheumatism 2757, 2762 (2006).

[40] App. 24, Wolfe & Michaud (2007) at 1433, 1439.

[41] App. 2, Askling et al. (2009) at 651-52.

TNF agents (relative risk of 1.0 (0.6 to 1.8), 1.35 (0.82 to 2.11) and 1.11 (0.51 to 2.37)."[42]

- **Haynes et al. (2013):** "In this large retrospective cohort study that included a broad spectrum of patients from multiple health plans throughout the US, we did not observe evidence of an increased risk of cancer [including lymphoma] associated with TNFα inhibitor therapy, either in an analysis limited to the period of current therapy or in an analysis that continued follow[-]up after the patient discontinued therapy."[43]

Likewise, when researchers pooled and analyzed data from the more than 70 clinical trials on Humira and other anti-TNFs in a series of meta-analyses,[44] they found that, considering the data as a whole, there was no increased risk of lymphoma associated with anti-TNFs:

- **Schiff et al. (2006):** This study reviewed data from the clinical trial safety database for 10,050 patients and 12,506 patient-years of exposure, and found that "long term adalimumab treatment is generally safe and well tolerated in patients with RA," and that the rate of lymphoma in individuals treated with Humira was "consistent with SIRs [standard incidence ratios] reported for RA populations naive to anti-TNF therapy."[45]

- **Leombruno et al. (2009):** This meta-analysis of eighteen randomized trials involving 8,808 rheumatoid arthritis patients concluded: "Our analysis showed that the risk of death, serious adverse events, serious infection, lymphoma, non-cutaneous cancer/melanoma or non-melanoma skin cancers was not increased with any anti-TNF at recommended doses."[46]

- **Mariette et al. (2011):** This meta-analysis of twenty-nine studies reported: "This systematic review and meta-analysis shows that TNFi [tumor necrosis factor inhibitors] treatments do not increase the risk of malignancy, particularly lymphoma."[47]

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[42] App. 15, Mariette et al. (2010) at 403.

[43] App. 11, Haynes et al., *Tumor Necrosis Factor α Inhibitor Therapy and Cancer Risk in Chronic Immune-Mediated Diseases*, 65 Arthritis & Rheumatism 48, 54 (2013).

[44] Meta-analysis combines "the results of numerous independent studies . . . in a statistically prescribed way" to provide a "pooled summary risk measure [that] is more precise with a narrower confidence interval (CI) than are separate estimates from individual studies." App. 50, Ory Expert Report at 6.

[45] App. 19, Schiff et al., *Safety Analyses of Adalimumab (HUMIRA) in Global Clinical Trials and US Postmarketing Surveillance of Patients with Rheumatoid Arthritis*, 65 Annals of the Rheumatic Diseases 889, 891 (2006).

[46] App. 13, Leombruno et al., *The Safety of Anti-Tumour Necrosis Factor Treatments in Rheumatoid Arthritis: Meta and Exposure-Adjusted Pooled Analyses of Serious Adverse Events*, 68 Annals of the Rheumatic Disease 1136, 1139 (2009).

[47] App. 16, Mariette et al. (2011) at 1903.

- **Singh et al. (2012):** This analysis of the Cochrane database, including 160 randomized trials with 48,676 participants and 46 extension studies with 11,954 participants, reported that there was "little or no difference in the number of people who experienced cancer [including lymphoma] while taking any biologic compared with people who took placebo," and in particular that the relative risk for lymphoma in Humira patients was less than 1.0.[48]

- **Burmester (2012):** This analysis of data from 71 global clinical trials involving 23,458 patients reported: "Overall malignancy rates for adalimumab-treated patients were as expected for the general population; the incidence of lymphoma was increased in patients with RA, but within the range expected in RA without anti-TNF therapy . . . ."[49]

- **Moulis et al. (2012):** This meta-analysis of thirty-three trials found "no excess risk of malignancies on anti-TNF-α . . . ," including specifically hematological cancers such as lymphoma.[50]

- **Lopez-Olivo et al. (2013):** This meta-analysis of sixty-three trials involving 29,423 patients found "[n]o statistically significant increased risk of developing malignancy [including lymphoma]," in patients taking anti-TNFs.[51]

In sum, a large body of data consistently shows that anti-TNFs ***do not*** increase lymphoma risk.

IV. Plaintiff's Experts Agree That There Are No Studies Showing Any Statistically Significant Association Between Anti-TNFs And Lymphoma.

These independent scientists are not alone in their assessment of the scientific evidence: plaintiff's experts under oath acknowledged these same basic scientific facts. For example, plaintiff's immunology expert Dr. Eric Gershwin agreed that, despite the "numerous" studies that had been conducted,[52] "there is . . . no full length peer reviewed epidemiologic study that showed

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[48] App. 21, Singh et al., *Adverse Effects of Biologics: A Network Meta-Analysis and Cochrane Overview (Review)*, 7 The Cochrane Library 3, 46 table 6 (2012).

[49] App. 9, Burmester et al., *Adalimumab: Long-Term Safety in 23[,]458 Patients from Global Clinical Trials in Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Psoriasis and Crohn's Disease*, 72 Annals of the Rheumatic Disease 1, 1 (2012).

[50] App. 17, Moulis et al., *Cancer Risk of Anti-TNF-alpha at Recommended Doses in Adult Rheumatoid Arthritis: A Meta-Analysis with Intention to Treat and per Protocol Analyses*, 7 PLOS ONE 1, 1, 4 (2012).

[51] App. 14, Lopez-Olivo et al., *Risk of Malignancies in Patients with Rheumatoid Arthritis Treated with Biologic Therapy - A Meta-analysis*, 308 JAMA 898, 904 (2012).

[52] App. 53, Gershwin *Calisi* Dep. at 74 (agreeing that "there have been numerous studies that have been conducted examining whether there's an increased risk of lymphoma or cancer in patients taking anti-TNF agents including

a statistically significant risk of lymphoma in general in patients taking anti-TNF therapy."[53] Moreover, he acknowledged that such studies were a pre-requisite to establishing causation, agreeing that "for someone to reach conclusions about cause and effect, you need a demonstrable association between exposure and disease."[54]

Consistent with this testimony, Dr. Gershwin previously published a review of the available literature and came to the same conclusion, stating: "***No causal link exists between TNF-α antagonists with lymphoma***."[55] Indeed, Dr. Gershwin noted that the rates of lymphoma reported in the literature "[were] actually lower than the annual incidence amongst the general population."[56] Dr. Gershwin acknowledged that "the *only* published research" that he had done on the topic states that "**there is no causal link between anti-TNF agents and lymphoma**.[57]

During his deposition in this case, Dr. Gershwin reiterated that the studies provide evidence that anti-TNFs may actually *reduce* the risk of lymphoma. For example, Dr. Gershwin conceded that "if the relative risk is less than one or the confidence interval includes values that are less than one, then that means that the exposure may actually be resulting in *less disease*"[58] and that here "there are *numerous studies* that have found confidence intervals where *the lower*

Humira"), 167 (same), 215 (agreeing that "there have been several meta-analyses on lymphoma risk in patients exposed to TNF inhibitors").

[53] *Id.* at 203.

[54] App. 53, Gershwin *Calisi* Dep. at 169; *see also id.* at 168 (agreeing that "you would look to epidemiology to answer the question of whether there has been an increased incidence of lymphoma in patients who were exposed to anti-TNF inhibitors."). Indeed, Dr. Gershwin agreed that "in order for there to be a risk of--or a positive relationship, there must be a relative risk above two." *Id.* at 169.

[55] App. 12, Kong et al. (2006) at 482 (emphasis added); *see also id.* at 478 ("[N]o clear evidence exists to causally link TNF-α antagonists with lymphoproliferative disease."); App. 55, Gershwin Dep. at 91-94 (agreeing that "despite [his] knowledge that TNF Alpha inhibitors could have immunologic effects [his] conclusion and take-home message that [he] wanted to communicate to physicians was that no causal link exists between TNF Alpha antagonists with lymphoma.").

[56] App. 12, Kong et al. (2006) at 478.

[57] App. 55, Gershwin Dep. at 95 (emphasis added).

[58] *Id.* at 169 (emphasis added); *see also Havner*, 953 S.W.2d at 723 (if a study "produce[s] a relative risk of 2.3" with a "confidence interval . . . of 0.8 and 3.2," the "results are . . . insignificant at the 95% level.").

bound goes below one."[59] In fact, he agrees that "*[a]ll of the studies*" of which he is aware "have confidence intervals for the . . . relative risk of lymphoma associated with anti-TNFs that go below one at the lower bound,"[60] a finding that he concedes is consistent with a *reduced* risk of lymphoma.[61]

Similarly, plaintiff's oncology expert, Dr. Dean McCracken, acknowledged during his deposition that there is "no study that's shown a statistically significant increased risk of lymphoma from anti-TNFs, including Humira,"[62] that "before you determine whether a pharmaceutical is causing a disease, you needed to establish that there's an association" and would "need multiple epidemiological studies" to do so,[63] that "there are reputable scientists who have concluded that there's no causal link between anti-TNFs and lymphoma,"[64] that based on the available data "it's not unreasonable to conclude that there's no causal link between anti-TNFs and lymphoma,"[65] and that in fact there is published data showing that "the incidence of lymphoma on patients—in patients on anti-TNFs based on the FDA data is actually lower than in the general population."[66] Accordingly, he is not aware of "any public health organization that's

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[59] App. 55, Gershwin Dep. at 443 (emphasis added); *see also id.* at 363 (agreeing that "there are people that have reduced risk of lymphoma because they're on anti-TNFs.").

[60] *Id.* at 445 (emphasis added).

[61] Dr. Gershwin is not alone in this conclusion. A number of researchers have noted that "TNF inhibitors could *decrease* the risk of cancer through suppressing inflammation and reducing angiogenesis." App. 22, Solomon, et al. (2012) at 21 (emphasis added); *see also, e.g.,* App. 15, Mariette et al. (2010) at 400 ("[A]nti-TNF therapy could reduce the inflammatory activity of the underlying disease, which is the main risk factor for lymphoma in RA."); App. 2, Askling et al. (2009) at 652 ("[t]he comparatively low and declining incidence of lymphoma among those starting anti-TNF therapy in 2002-6 might suggest a *beneficial effect* of anti-TNF therapy on lymphoma occurrence in RA." (emphasis added)).

[62] App. 62, McCracken Dep. at 150-151, 168-69.

[63] *Id.* at 133. Dr. McCracken agreed that generally you would need a "relative risk of at least 2 in the epidemiologic studies." *Id.* at 137-38.

[64] *Id.* at 66.

[65] *Id.* at 66-67.

[66] *Id.* at 58-59, 158-59 (observing that the Askling study among others reported "a decrease in risk over time of lymphoma in patients on anti-TNFs" and that he cited studies in his report that showed "that anti-TNFs are

concluded that Humira causes lymphoma," "none of the articles" he cites in his report "say that Humira causes lymphoma," and in particular he is "not aware of any statement by the FDA that Humira causes lymphoma."[67]

ARGUMENT

I. Abbott Is Entitled To Summary Judgment On All Claims Because There Is No Evidence That Humira Caused Ms. Murthy's Lymphoma.

To prevail on her claims, "plaintiff must demonstrate both general causation and specific causation." *Burton v. Wyeth-Ayerst Labs. Div. of Am. Home Prods. Corp.*, 513 F. Supp. 2d 719, 729 n.13 (N.D. Tex. 2007). To do so, she "must prove that [Humira] is capable of causing the specific injury of which she complains," and "secondly . . . that her injury was caused by [Humira]." *See id.*; *accord*, *e.g.*, *Wells v. Smithkline Beecham Corp.*, 601 F.3d 375, 377-78 (5th Cir. 2010). As demonstrated by the scientific evidence and admitted by her own experts, plaintiff can satisfy neither requirement.[68]

A. Plaintiff Cannot Meet Her Burden To Demonstrate General Causation.

This Court has previously held that Texas law governs this diversity jurisdiction case. *See Murthy v. Abbott Labs.*, 847 F. Supp. 2d 958, 967 (S.D. Tex. 2012). Applying the rigorous requirements for demonstrating causation under Texas law, plaintiff's claims are plainly barred.

In *Havner*, the Texas Supreme Court imposed strict limitations on the type of scientific evidence that may be used to prove causation in a toxic tort case. Because it addressed an issue of sufficiency of evidence (*i.e.*, what constitutes "more likely than not burden of proof"), *see* 953

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associated with a decreased risk"), 251 (acknowledging that the Moulis study is "consistent with a decreased risk of hematological cancer from anti-TNFs.").

[67] *Id.* at 161.

[68] "Causation is a necessary element of all of [plaintiff's] claims." *Centocor, Inc. v. Hamilton*, 372 S.W.3d 140, 170 n.31 (Tex. 2012) (addressing a pharmaceutical failure-to-warn plaintiff's strict liability, negligence, gross negligence, fraud, and malice claims); App. 25, Murthy HERO Informed Consent Form, at 7 (Murthy entitled to compensation under contract only if she was injured "as a direct result" of her participation in HERO, a Humira clinical trial).

S.W.2d at 717, *Havner* is substantive Texas law and controls in determining whether a diversity-jurisdiction plaintiff has met her causation burden. *See Cotroneo v. Shaw Envtl. & Infrastructure, Inc.*, 639 F.3d 186, 192-93 (5th Cir. 2011) (applying *Havner* to find "plaintiffs' evidence . . . insufficient to raise a genuine issue of fact as to whether there was a causal connection between the radiation exposure and the plaintiffs' claimed injuries.").[69] Plaintiff does not come close to clearing *Havner*'s high hurdle.

Havner reversed a jury verdict for plaintiffs who claimed that the drug Bendectin caused birth defects, finding it unsupported by evidence. 953 S.W.2d at 730. In so doing, the Texas Supreme Court set out requirements for courts to apply in determining the sufficiency of epidemiologic causation evidence. The court held that to "to raise a fact issue on whether [the substance] caused" the injury, *id.* at 714, an epidemiologic study must at a minimum: (1) demonstrate "more than a doubling of the risk" (that is, a relative risk of over 2.0); (2) not include a confidence interval of 1.0; and (3) have a confidence level of at least 95%. *Id.* at 717-18, 724-25. Once these threshold requirements are met, the court must further examine the study using factors such as the Bradford Hill criteria, because "association does not equate to causation" and "[t]here may in fact be no causal relationship even if the relative risk is high." *Id.* at 718, 724. At least two such statistically significant and reliable studies are required. *Id.* ("We do not hold . . . that a single epidemiological test is legally sufficient evidence of causation.").

The Texas Supreme Court reemphasized these requirements just two years ago in *Garza*. Siding with plaintiffs, the lower appellate court had concluded that *Havner* did not

[69] *See also Cano v. Everest Minerals Corp.*, 362 F. Supp. 2d 814, 821 (W.D. Tex. 2005) ("whether a Plaintiff's proffered evidence amounts to . . . legally sufficient evidence . . . of causation is a question of Texas substantive law, and thus *Havner* controls on that issue."); *Burton*, 513 F. Supp. 2d at 729 n.12 ("agree[ing] with . . . other federal courts that have addressed the issue: *Havner*'s standards are substantive, not procedural, requirements."); App. 107, *Wells v. SmithKline Beecham Corp.*, No. A-06-CA-126-LY, 2009 WL 564303, at *8 (W.D. Tex. Feb. 18, 2009) ("*Havner* establishes substantive Texas law on a plaintiff's causation burden of proof.") (collecting cases), *aff'd,* 601 F.3d 375 (5th Cir. 2010).

"establish[] . . . a bright-line test for causation," and permitted plaintiffs to rely on a "totality of the evidence" approach to establish causation despite a lack of statistically-significant studies that satisfied *Havner*. 347 S.W.3d. at 260, 267. The Texas Supreme Court reversed, explaining that in order to establish causation under *Havner*, plaintiffs must offer at least two reliable studies that "demonstrate a statistically significant doubling of the risk":

> *Havner* holds, and ***we reiterate***, that when parties attempt to prove general causation using epidemiological evidence, ***a threshold requirement of reliability is that the evidence demonstrate a statistically significant doubling of the risk***. [. . .] *Havner* also requires that even if studies meet the threshold requirements of reliability, sound methodology still necessitates that courts examine the design and execution of epidemiological studies using factors like the Bradford Hill criteria to reveal any biases that might have skewed the results of a study, and to ensure that the standards of reliability are met in at least two properly designed studies. Thus, ***a plaintiff must first pass the primary reliability inquiry by meeting Havner's threshold requirements of general causation.*** Then, courts must conduct the secondary reliability inquiry that examines the soundness of a study's findings using the totality of the evidence test.

Id. at 265-66 (emphases added) (footnotes omitted); *see also id.* at 264 ("*Havner*'s requirements necessarily apply to all epidemiological evidence"). *Garza* thus makes clear that "[t]he totality of the evidence cannot prove general causation if it does not meet the standards for scientific reliability established by *Havner*" because "[a] plaintiff cannot prove causation by presenting different types of unreliable evidence." *Id.* at 268.[70]

Plaintiff cannot meet the *Havner* and *Garza* tests because she cannot point to a single epidemiological study demonstrating a doubling of risk from anti-TNF treatments, let alone two. Plaintiff's sole general causation expert, Dr. Gershwin, concedes that these requirements cannot be met here, acknowledging that despite "numerous" studies, "there is . . . no full length peer

[70] At least one pre-*Garza* decision had made the same error as the *Garza* appellate court, interpreting *Havner* to mean that "[t]here is no requirement in a toxic tort case that a party must have reliable epidemiological evidence of a relative risk of 2.0 or greater." *Minnesota Mining & Mfg. Co. v. Atterbury*, 978 S.W.2d 183, 198 (Tex. App. 1998). But as *Garza* explained, "a plaintiff must *first* pass the primary reliability inquiry *by meeting Havner's threshold requirements of general causation*" before the court will consider the "totality of the evidence," and "plaintiff cannot prove causation by presenting different types of unreliable evidence." 347 S.W.3d at 265-66, 268 (emphasis added).

reviewed epidemiologic study that showed a statistically significant risk of lymphoma in general in patients taking anti-TNF therapy."[71] By his own admission, Dr. Gershwin's opinion thus fails the *Havner*/*Garza* standard, and the lack of epidemiologic evidence showing that Humira at least doubles the risk of lymphoma is fatal to plaintiff's claims. *See, e.g.*, *Cotroneo*, 639 F.3d at 192-93 (affirming summary judgment for defendant where plaintiffs failed to meet *Havner* requirements and thus failed to "raise a genuine issue of fact" on causation); *Havner*, 953 S.W.2d at 724-30 (declining to consider non-statistically significant studies, *in vivo* and *in vitro* animal studies, and a chemical structure analysis as evidence of causation); *Garza*, 347 S.W.3d at 267 (finding that plaintiff's epidemiologic studies that purportedly showed a doubling of the risk did not satisfy *Havner*, and rejecting the argument that "the totality of the evidence in this case shows general causation").[72]

Indeed, the epidemiology here conclusively refutes plaintiff's causation claims because the studies consistently find no statistically significant relationship between anti-TNFs and lymphoma.[73] As a result, there is "strong evidence that lymphoma is not increased among RA

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[71] App. 53, Gershwin *Calisi* Dep. at 74, 203. Plaintiff's specific causation expert, Dr. McCracken, agreed, acknowledging that there is "no study that's shown a statistically significant increased risk of lymphoma from anti-TNFs, including Humira," and that "before you determine whether a pharmaceutical is causing a disease, you needed to establish that there's an association" and would "need multiple epidemiological studies" to do so. (App. 62, McCracken Dep. at 150-51, 133.)

[72] *See also* App. 107, *Wells*, 2009 WL 564303, at *10-12 (granting summary judgment against a plaintiff who claimed that prescription drug Requip (ropinirole) caused his pathological gambling, where "[n]one of [plaintiff's] experts' reports include[d] *Havner*-required statistics" and plaintiffs' experts "conceded at their depositions that statistically reliable studies finding an association between ropinirole and pathological gambling do not exist . . . "); App. 74, *Current v. Atochem N. Am., Inc.*, No. W-00-CV-332, 2001 WL 1875950, at *1 (W.D. Tex. Dec. 17, 2001) (granting summary judgment for defendant because "[p]laintiffs have failed to meet the *Havner* burden."); *Brookshire Bros. v. Smith*, 176 S.W.3d 30, 37-39 (Tex. App. 2004) (applying *Havner* to reverse verdict for plaintiff and direct judgment for defendant where plaintiff's expert "did not refer to a single epidemiological study or scientific article to prove that exposure to commercial cleaners can cause [plaintiff's injury]"); *Daniels v. Lyondell-Citgo Refining Co.,* 99 S.W.3d 722, 728-30 (Tex. App. 2003) (affirming summary judgment for defendant and finding "no evidence of general causation" where "[n]one of [plaintiff's] studies ha[d] the *Havner* requisite risk-doubling.").

[73] *See supra* Background § III.

patients treated with anti-TNF agents,"[74] and a series of meta-analyses (which analyze pooled data from over seventy trials on Humira and other anti-TNFs) confirm that there is no association between anti-TNF therapy and this disease.[75] Thus, this is not a case in which plaintiff has merely failed to produce the required epidemiologic evidence. Rather, it is a case where epidemiologic evidence affirmatively and uniformly refutes plaintiff's causation claims. Even absent the stringent requirements of *Havner* and *Garza*, plaintiff's claims would be barred.[76]

B. Plaintiff's Experts Provide No Evidence Of General Causation At All.

Indeed, at bottom, plaintiff has not even attempted to offer expert evidence to establish general causation—a critical prerequisite of her claims. To the contrary, plaintiff's sole general causation expert, Dr. Gershwin, concedes that the scientific evidence here does ***not*** meet his own requirements for establishing causation.[77] Thus, when he addressed the question in his published work, he concluded: "***No causal link exists between TNF-α antagonists with lymphoma***."[78]

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[74] App. 24, Wolfe & Michaud (2007) at 1439; *see also, e.g.*, App. 22, Solomon, et al. (2012) at 29 ("[W]e observed (in our review) a consistent lack of association between TNF inhibitors and cancer . . . ."); App. 10, Cush, et al. (2012) at 2 (reporting that there is no evidence that anti-TNFs "impart an added risk of lymphoma.").

[75] *See supra* Background § III.

[76] *See, e.g.*, *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1315 (11th Cir. 1999) (excluding expert opinion "in direct contrast to over twenty other epidemiological studies that found no statistical correlation between silicone breast implants and systemic disease"); *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 24-25 (1st Cir. 2011) (observing that federal courts routinely exclude contrary expert opinion where "the available epidemiological studies found that there is no causal link"); *see generally* Def.'s Mot. to Exclude Causation Testimony.

[77] As Dr. Gershwin acknowledged, "to reach conclusions about cause and effect, you need a demonstrable association between exposure and disease"; that "for there to be a risk of . . . a positive relationship, there must be a relative risk above two"; and that "if the relative risk is less than one or the confidence interval includes values that are less than one, then that means that the exposure may actually be resulting in less disease[.]" App. 53, Gershwin *Calisi* Dep. at 169. Yet, Dr. Gershwin concedes that plaintiff lacks even a single full-length, peer-reviewed study finding a statistically-significant association between Humira and lymphoma. *Id.* at 203.

[78] App. 12, Kong et al. (2006) at 482 (emphasis added); *see also id.* at 478 ("[N]o clear evidence exists to causally link TNF-α antagonists with lymphoproliferative disease."); App. 55, Gershwin Dep. at 91-94 (agreeing that "despite [his] knowledge that TNF Alpha inhibitors could have immunologic effects [his] conclusion and take-home message that [he] wanted to communicate to physicians was that no causal link exists between TNF Alpha antagonists with lymphoma").

Rather, as Dr. Gershwin made clear in his deposition testimony, his opinions in this case "focus[] entirely" on *biological plausibility*[79] (*i.e.*, whether there is some plausible theoretical mechanism by which lymphoma might occur), one of the Bradford-Hill factors used by epidemiologists to evaluate the strength of an association in an epidemiologic study *after* competent epidemiological studies have demonstrated that an association in fact exists. As the Texas Supreme Court recognized in *Havner*, in the absence of such a demonstrated association, biologic plausibility (or any other Bradford-Hill factor) does not constitute independent evidence of causation at all. Rather, such factors are used only ***after*** a plaintiff has met the threshold requirement to produce studies demonstrating a statistically significant association between the substance and the claimed injury. *See Havner*, 953 S.W.2d at 718-19 & n.2; *Garza*, 347 S.W.3d at 266; App. 107, *Wells*, 2009 WL 564303, at *6 ("*Havner* . . . states that if a plaintiff's expert bases his opinion on scientifically reliable epidemiological studies, he should ***then*** consider other factors, such as the application of the Bradford Hill criteria.") (emphasis added), *aff'd*, 601 F.3d 375 (5th Cir. 2010).[80] In fact, this has long been Texas law, which recognizes that under *Havner*,

[79] App. 53, Gershwin *Calisi* Dep. at 360 ("My report and everything I do is focused ***entirely*** on biologic plausibility.") (emphasis added); *id.* at 364 (" . . . I haven't even looked at any papers relating to any cancers and certainly not any epidemiologic papers."); *id.* at 219 (Epidemiological studies are "not the basis of my opinions. The basis of my opinions is biologic plausibility and mechanisms of action."); App. 55, Gershwin Dep. at 164 ("[T]he opinions that I offer relate to mechanisms of action in the use of anti-TNF. They don't relate to epidemiology.").

[80] *See also, e.g.*, App. 80, *Frischhertz v. SmithKline Beecham Corp.*, Civ. No. 10-2125, 2012 WL 6697124, at *3 (E.D. La. Dec. 21, 2012) ("[t]he Bradford-Hill criteria can ***only*** be applied ***after*** a statistically-significant association has been identified.") (emphasis added); *id.* (excluding expert who "attempted to use the Bradford-Hill criteria to prove causation without first identifying a valid statistically-significant association."); *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 678 (M.D.N.C. 2003) (agreeing that "Bradford Hill criteria is a method for determining whether the results of an epidemiological study can be said to demonstrate causation and not a method for testing an unproven hypothesis."); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 569 (W.D. Pa. 2003) ("[B]ecause plaintiff's experts have not demonstrated any statistically-significant epidemiologic study showing an increased risk of postpartum stroke in women using Parlodel, application of the Bradford-Hill criteria is unwarranted.") (citing *Havner*, 953 S.W.3d at 718-19). Indeed, the Bradford-Hill criteria themselves make clear that they may only be used ***after*** an observed association, as it would be impossible to apply several of those criteria otherwise. *See Havner*, 953 S.W.2d at 718 n.2 (listing "strength of *association*," "consistency of *association*," and "[s]pecificity [of *association*]" as the first three criteria) (emphasis added); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1233 n.5

"[p]lausibility is not enough." *Exxon Corp. v. Makofski*, 116 S.W.3d 176, 187 (Tex. App. 2003).[81]

Plaintiff's expert, Dr. Gershwin, concurs with this judgment. As he acknowledged in his deposition, "biological plausibility alone does not prove causation[.]"[82] And far from providing an unequivocal opinion that the mechanism of the anti-TNF inhibitors could only lead to an increased risk of lymphoma, he concedes that it is "biologically plausible that anti-TNFs ***reduce*** the risk of lymphoma."[83] Dr. Gershwin's "biologic plausibility" theory does not even purport to establish causation both by his own admissions and as a matter of well-settled Texas law.[84]

C. Plaintiff Cannot Meet Her Burden to Demonstrate Specific Causation.

Plaintiff's failure to establish general causation bars her claims and the Court need not proceed further, because "a plaintiff must establish general causation before moving to specific causation. Without the predicate proof of general causation, the tort claim fails." *Wells*, 601

(D. Colo. 1998) ("The Bradford-Hill criteria *start* with an association demonstrated by epidemiology . . . .") (emphasis added).

[81] *Havner* explained that expert "testimony . . . that a substance 'could' or 'can' cause a disease or disorder is not evidence that in reasonable probability it does," and that: "[t]he fact that Bendectin *may* have an adverse effect on limb bud cells is the beginning, not the end of the scientific inquiry and proves nothing about causation without other scientific evidence." 953 S.W.2d at 729-30 (citation and internal quotation marks omitted, emphasis added). Decisions from other jurisdictions are in accord. *See, e.g.*, *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1295-96 (M.D. Fla. 2007) ("a biological explanation without evidence of the mechanism by which it works is merely an unproven hypothesis, a theory," and "[w]hile [the expert's] biological theory may be exactly right, at this point it is merely plausible, not proven, and biological possibility is not proof of causation."); App. 85, *In re Bausch & Lomb, Inc. Contact Lens Solution Prods. Liab. Litig.*, MDL No. 1785, 2009 WL 2750462, at *12 (D.S.C. Aug. 26, 2009) ("biological plausibility is insufficient to demonstrate causation.").

[82] App. 53, Gershwin *Calisi* Dep. at 416; *id.* at 417 ("[B]iological plausibility is necessary but not sufficient to establish causation."); *id.* at 178 (agreeing that "biological plausibility by itself doesn't establish causation[.]").

[83] *Id.* at 363-64 (emphasis added); *see also id.* at 196 (agreeing that "[f]rom a mechanistic standpoint, it can be hypothesized that the inhibition of TNF could either enhance or inhibit cancer development" and that "it's biologically plausible that TNF therapy could either inhibit or enhance the development of lymphoma[.]").

[84] *Havner* imposes yet another requirement for causation evidence to pass muster, and it is yet another requirement that plaintiff cannot satisfy here. Specifically, even after coming up with *Havner*-acceptable studies, plaintiff must still "show that he or she is similar to those in the studies," which requires "proof that the injured person was exposed to the same substance, that the exposure or dose levels were comparable to or greater than those in the studies, that the exposure occurred before the onset of injury, and that the timing of the onset of the injury was consistent with that experienced by those in the study." 953 S.W.2d at 720. Here, plaintiff has offered ***no*** studies that satisfy *Havner* and, axiomatically, cannot meet these additional requirements either.

F.3d at 378. Nonetheless, the testimony of plaintiff's specific causation expert, Dr. McCracken, makes clear that plaintiff cannot demonstrate specific causation either.

Havner holds that "if there are other plausible causes of the injury or condition that could be negated, the plaintiff must offer evidence ***excluding those causes with reasonable certainty***." 953 S.W.2d at 720 (emphasis added). A plaintiff's failure to do so dooms her case. *Cotroneo*, 639 F.3d at 193 (citing *Havner* and affirming summary judgment because plaintiffs "have not offered evidence excluding other plausible causes of their injuries with reasonable certainty.").

While Dr. McCracken claimed in his report that he had "consider[ed]" several potential causes of plaintiff's lymphoma and "attempt[ed] to rule in or rule out these various factors,"[85] his deposition revealed that he in fact did nothing of the sort, and his purported differential diagnosis was nothing more than *ipse dixit*.[86] Dr. McCracken admitted that he "***[c]annot*** rule out [the] possibility" that plaintiff's lymphoma was caused by any of several potential causes other than Humira, including: (1) RA alone[87]; (2) idiopathic causes (which may include "[i]ndividual . . . genetics" and "environmental exposures"); (3) RA treatments other than anti-

[85] Dkt. 123-1, McCracken Report at 2.

[86] Texas law does not "accept the expert's opinion as . . . evidence simply because he used the magic words" like "reasonable medical probability[,]" and instead requires a careful evaluation of the expert's "testimony in its entirety[.]" *Havner*, 953 S.W.2d at 711 (citation and quotation marks omitted); *see also id.* at 712 (declining to reduce the court's review "to a meaningless exercise of looking to see only what words appear in the transcript of the [expert's] testimony"). Dr. McCracken's bald assurance that he "consider[ed]" several causes of plaintiff's lymphoma cannot stave off summary judgment. *See, e.g.*, *Coastal Transp. Co., v. Crown Ctr. Petroleum Corp.*, 136 S.W.3d 227, 232 (Tex. 2004) (an expert's "bare conclusions d[o] not amount to any evidence at all") (citation and quotation marks omitted); App. 70, *Baker v. Smith & Nephew Richards, Inc.*, No. 95-58737, 1999 WL 811334, at *33 (Tex. Dist. Ct. June 7, 1999) (unpublished) (an expert's "magic words" that his "opinion is based on . . . the elimination of other potential causes" is not enough; he must "specifically describe each possible cause, the exact process used to eliminate other potential causes, and the reliability of the [expert's] identification of the other possible causes and their elimination[.]"), *aff'd sub nom.*, App. 96, *McMahon v. Smith & Nephew Richards, Inc.*, No. 14-99-00616CV, 2000 WL 991697 (Tex. App. July 20, 2000) (unpublished).

[87] Dr. McCracken admitted that plaintiff's moderate RA alone could have caused her lymphoma, that it is "not uncommon" for RA itself to cause lymphoma, that moderate RA is "associated with an eight-fold increase" in lymphoma risk, and that "high overall disease activity" is "associated with a 70-fold increase[.]" App. 62, McCracken Dep. at 94-95, 100.

TNFs; or (4) age.[88] Dr. McCracken also conceded that there is ***no*** methodology that can "distinguish between lymphomas caused by anti-TNFs versus those caused by other causes, including idiopathic causes[.]"[89] And he admitted that he did not even attempt to "calculate a numerical relative risk for any factors . . . that could have contributed to [plaintiff's] lymphoma" here, that "most of the causes of lymphoma are . . . idiopathic or unknown," [90] and that ***"[p]robably higher" than "80 or 90 percent*** of lymphomas are idiopathic."[91] Dr. McCracken has thus not ruled out alternative causes "with reasonable certainty" (or otherwise), and his specific causation opinion—and plaintiff's claims—fail as a result.

Moreover, because Dr. McCracken admits that (1) plaintiff's RA alone increases her risk of lymphoma by up to eight-fold, (2) he cannot rule out multiple other causes as potential sole causes, and (3) over 80 or 90% of lymphomas are idiopathic,[92] as a matter of simple arithmetic there is ***no*** basis to conclude that plaintiff's lymphoma was "more likely than not" attributable to Humira as Texas law requires.[93] In light of *Havner*'s clear directive that "[o]ur legal system requires that claimants prove their cases by a preponderance of the evidence," 953 S.W.2d at 728, Dr. McCracken's admissions mandate summary judgment for Abbott. *See, e.g.*, *Cotroneo*, 639 F.3d at 193 (affirming summary judgment under *Havner*); *Cano*, 362 F. Supp. 2d at 840 (finding expert's causation opinion "no[t] relevant" under *Havner* because he "failed to

[88] *Id.* at 164-65.

[89] *Id.* at 106; *see also id.* at 112-13 (conceding that it is "impossible" to determine "whether a patient's lymphoma was caused by idiopathic causes.").

[90] *Id.* at 125.

[91] *Id.* at 98 (emphasis added); *see also id.* at 98 (testifying that "most patients are idiopathic."); *id.* at 164 (agreeing that he "would expect there would be many patients on anti-TNFs, including Humira, who develop lymphoma for reasons that don't have anything to do with anti-TNFs" and that "just because someone received Humira and developed Humira does not mean that their lymphoma was caused by Humira").)

[92] *Id.* at 94-95, 100, 166, 165, 98.

[93] *See Cano*, 362 F. Supp. 2d at 840 ("Consistent with federal law, . . . Texas substantive law states that a cause becomes 'probable' only when in the absence of other reasonable causal explanations it becomes more likely than not that the injury was a result.") (citation and internal quotation marks omitted).

adequately rule out other causes" and could not "quantify his alleged risk factors" for plaintiffs' cancer); *Weiss v. Mech. Assoc. Servs., Inc.*, 989 S.W.2d 120, 125-26 (Tex. App. 1999) (affirming judgment for defendant because "a bare expert opinion" on causation is not enough, and a review of the testimony of plaintiff's experts showed that "none of [the experts] . . . were able to rule out other potential causes of [plaintiff's] illness with reasonable certainty.").[94]

[94] *See also, e.g.*, *Wackman v. Rubsamen*, 602 F.3d 391, 400 (5th Cir. 2010) (citing *Havner* and holding that "a plaintiff must rule out other plausible causes of the injury."); *Mobil Oil Corp. v. Bailey*, 187 S.W.3d 265, 274-75 (Tex. App. 2006) (finding, under *Havner*, insufficient evidence that asbestos exposure caused decedent's lung cancer because plaintiffs' experts did not exclude other plausible causes such as smoking with reasonable certainty); *Exxon*, 116 S.W.3d at 188-89 (finding insufficient evidence under *Havner* that benzene caused decedent's anemia because plaintiff's expert did not exclude other plausible causes); *Guinn v. AstraZeneca Pharm. LP*, 602 F.3d 1245, 1256-57 (11th Cir. 2010) (affirming summary judgment in case alleging Seroquel caused plaintiff's diabetes by causing her weight gain where the expert, among other things, had not ruled out plaintiff's other diabetes risk factors, agreed other factors may have been sufficient to explain her diabetes, and did not determine relative risk of each factor); *Conde v. Vesicol Chem. Corp.*, 24 F.3d 809, 810, 814 (6th Cir. 1994) (affirming summary judgment on grounds that plaintiffs' expert testimony, "even if it were admissible, . . . was insufficient to allow a jury to conclude . . . that [plaintiffs] suffered personal injuries as a result of their exposure to chlordane" where, among other things, experts were "unable to exclude other potential causes for these symptoms"); *Haller v. AstraZeneca Pharm. LP*, 598 F. Supp. 2d 1271, 1306 (M.D. Fla. 2009) (granting summary judgment where "[plaintiff's expert's] testimony [was] sufficient only to raise the *possibility* that Seroquel caused [plaintiff's] diabetes" and where, "given all of the possible and equally plausible causes of [plaintiff's] diabetes . . . no reasonable jury could conclude that Seroquel was the 'but for' cause of, or even a factor that contributed *substantially to*, diabetes in [plaintiff]."); *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1485 (D.V.I. 1994) (granting summary judgment in a case alleging that asthma medication caused birth defects, where plaintiff's experts had "not excluded or [could not] exclude" various potential other causes, including "those unknown events that cause the great majority of birth defects," and those opinions were thus "insufficient to sustain a jury verdict in plaintiff's favor.").

CONCLUSION

For all of the foregoing reasons, as well as the reasons stated in Abbott's accompanying motions to exclude the testimony of plaintiff's experts, Abbott respectfully requests that the Court enter an order dismissing plaintiff's claims and granting summary judgment in its favor.

Dated: July 9, 2013

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on July 9, 2013, I electronically filed the foregoing document with the clerk of court for the U.S. District Court, Southern District of Texas, using the electronic case filing system of the court. The electronic case filing system sent a "Notice of Electronic Filing" to the following attorneys of record who are known "Filing Users":

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